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Generation of Aerosolized Drugs

R.K. WOLFF[1] and R.W. NIVEN[2]

[1]*Toxicology Research Laboratories, Lilly Research Laboratories*
A Division of Eli Lilly and Company
P.O. Box 708
Greenfield, IN 46140
[2]*Amgen*
1840 Dehavilland Drive
Thousand Oaks, CA 91320

ABSTRACT

The expanding use of inhalation therapy has placed demands on current aerosol generation systems that are difficult to meet with current inhalers. The desire to deliver novel drug entities such as proteins and peptides, as well as complex formulations including liposomes and microspheres, requires delivery systems of improved efficiency that will target the lung in a reproducible manner. These efforts have also been spurred by the phase out of chlorofluorocarbons (CFCs) and this has included a directed search for alternative propellants. Consequently, a variety of new aerosol devices and methods of generating aerosols are being studied. This includes the use of freon replacement propellants, dry powder generation systems, aqueous unit spray systems and microprocessor controlled technologies. Each approach has advantages and disadvantages depending upon each principle of action and set of design variables. In addition, specific drugs may be better suited for one type of inhaler device vs. another. The extent to which aerosol generation systems achieve their goals is discussed together with a summary of selected papers presented at the recent International Congress of Aerosols in Medicine.

BACKGROUND

a) Impetus for New Medical Aerosol Devices

The generation of aerosolized drugs has been dominated by pressurized metered dose inhalers (MDIs). These inhalers offer consistent dose delivery in a highly convenient and robust canister system, and they have been the delivery system of choice for inhaled pharmaceuticals for the out-patient treatment of asthma over the last three decades (Newhouse, 1991). The propellants used in these inhalers are usually a mixture of chlorofluorocarbons (Sanders, 1970; Hallworth, 1987; Byron, 1990). Therefore, because of the proposed phaseout of these chemicals under the Montreal Protocol (Manzer, 1990; Coyne, 1991; Reg. Affairs J, 1993), there has been considerable impetus toward searching for alternative delivery devices (Matthys, 1991; Daly, 1993).

The biotechnology revolution has also fueled interest in pulmonary delivery of drugs. Recombinant DNA technology has made it possible to produce many recombinant proteins and peptides of potential therapeutic application. However, most proteins and peptides are poorly absorbed when administered via the oral route which is the preferred

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route for pharmaceutical use. There are data indicating that proteins can be absorbed from the respiratory tract - both from the nose and the lung (O'Hagan and Illum, 1990; Platz and Patton, 1993). Patton et al. (1993) and Colthorpe et al. (1993) have shown that many proteins are well absorbed from the lung. The early work of Wigley et al. (1971) has been extended to humans by Laube et al. (1993) and they have shown, for the particular case of insulin, that the pulmonary absorption of inhaled aerosol is quite high and a marked lowering of blood glucose is achieved. Adjei (1993) also demonstrated that the site of deposition and method of generation can dramatically affect the eventual bioavailability. One of the major challenges is to improve the delivery efficiency of the aerosol generation devices so that deposition is optimized while wastage is minimized. Another formulation challenge is to avoid degradation of the biological activity of the protein or peptide. Agents such as liposomes are being considered for topical delivery of pharmaceuticals (Mihalko et al., 1988; Niven and Schreier, 1990) and they may have some capacity to protect their encapsulated drug.

The pressurized MDIs are highly successful aerosol delivery devices but have shortcomings that are inherent from their basic design. Metered dose inhalers currently dispense precise volumes of pressurized chlorofluorocarbon (CFC) propellants from a metering valve and actuator. Following release by the actuator, breakup of the liquid droplets appears to be primarily the result of volatilization of the CFC propellant (Hallworth, 1987). This mode of action gives rise to a high velocity plume (25-50 m/s), which is expelled 20-30 cm into free air (Hallworth, 1987; Byron, 1990). Thus, significant deposition of drug in the mouth and throat can be expected. This has been confirmed by extensive studies in patients using radiolabeling techniques, where Tc-99m (eg as Tc-99m-HSA) tagged to drug particles has allowed deposition patterns in the respiratory tract to be visualized by gamma camera scintigraphy (Dolovich et al., 1981, 1989; Newman et al., 1981, 1982, 1985). The deposition pattern is influenced by the high velocity of the aerosol jet as well as the fact that there are 10-20 μm particles present in the jet as it reaches the mouth (Newman et al., 1982). Figure 1 illustrates that oral deposition is high (approximately 80-90%) with MDIs despite using the recommended inhalation technique. (A full exhalation, coordination of the actuation with inspiration, followed by a slow deep inhalation and finally a breath hold for several seconds).

Figure 1. Gamma camera scintigraphy of deposition following use of a pressurized MDI in a human subject (Newman et al., 1981).

Lung deposition of only approximately 10% of the actuated dose is typical for subjects inhaling from MDIs, although variability is high and deposition can range from 0 to 30%. This has been demonstrated in numerous studies (Dolovich et al., 1981; Newman et al., 1985; Wilson, 1987). Deposition in the lung is optimized by controlling the particle size so that the mass median aerodynamic diameter (MMAD) of aerosols is in the 1-5 μm range (Moren, 1985; Newhouse and Dolovich, 1987; Swift, 1989) as is achieved for most pressurized MDIs (Hiller et al., 1980; Kim et al., 1987; Velasquez, 1990). Because pressurized MDIs usually contain suspensions of pharmaceuticals stabilized by surfactant in a propellant blend, this means that the actuated particle size is ultimately limited by the size of the solid ingredients. Jet-milling of particles below 3 μm is difficult (Grassel, 1976; Hinds, 1979; Cheng et al., 1985), and milled particles are present in most current pressurized MDIs. Spray drying can extend this range to less than 1 μm if necessary, through adjustment of the spray conditions, particularly droplet size and solution concentration (Masters, 1991) and it is expected that this process will be employed more frequently in the future.

Jet-nebulizers also give reasonable lung deposition under favorable conditions and they extend the range of drugs that can be administered by aerosolization. Since dose is administered on a continuous basis instead of as a bolus, there can be compliance issues together with significant wastage of drug in the reservoir and tubing. Overall, the fraction of dose reaching the lung may be less than that achieved by pressurized MDIs (Fuller et al., 1990) and there is room for improvement, especially toward minimizing reservoir wastage. However, despite the lower delivery efficiency of the jet nebulizer, clinical responses are often similar, but achieved by using a higher reservoir dose.

b) Generation Methods

The common types of aerosol generation devices are shown in Figure 2. Air-jet nebulizers all work on the principle shown in Figure 2a. A compressed air source is used to create a high velocity air-jet through an orifice. As the gas expands beyond the nozzle, a low pressure region is created and this serves to draw solution from a capillary tube connected to a liquid reservoir. The water stream from the capillary tube is sheared into unstable filaments and droplets as it exits the tube, creating the aerosol. A range of configurations, flow rates, and baffle types is possible that strongly influence the performance characteristics of any given nebulizer (Lefebvre, 1989).

A schematic of a pressurized metered dose inhaler is shown in Figure 2b. CFCs, pharmaceutical, and excipients are contained in a canister as a liquefied compressed gas mixture. The actuation of the metering valve releases the mixture and aerosol is released as described above.

Ultrasonic nebulizers operate by the application of high frequency electrical energy to a piezoelectric transducer that converts the electrical energy to mechanical energy in a vibrational mode. This energy is transmitted directly to the pharmaceutical suspension or solution or through a coupling fluid (Figure 2c).

Dry powder generation is generally more difficult to perform in a controllable and consistent manner than liquid aerosol generation. Various dry powder generation methods (Grassel, 1976; Hinds, 1979) have been used in inhalation toxicology applications including Wright Dust Feeders (Wright, 1950), air jet mills (Cheng et al., 1985), and fluidized beds (Yeh et al., 1988). These methods usually entail some method, such as a scraper blade or an air blast, to break up particles from a container and then employ a carrier air stream to transport the aerosol to the intended destination. Figure 2d shows a schematic of a Wright Dust Feeder which is often used as an aerosol generator to provide exposure atmospheres for laboratory animals in toxicology studies. In current dry powder inhalers the deaggregating force, and the air flow are provided solely by the inspiration of the patient. This has advantages in terms of simplicity but it also means that aerosol characteristics are dependent on the patient's inhalation and not the performance of the device. The problem of generating the aerosol is compounded by the fact that the aerosol particles are pre-made and then compacted into a small, portable device. It is therefore no surprise that the patient is unable to generate sufficient inspiratory force to completely dispense and deaggregate the powdered dose.

Sprays are produced by forcing pharmaceutical suspensions or solutions through a nozzle under pressure (Figure 2e). Output and particle size are dependent on nozzle size and configuration, the applied pressure, and the liquid feed rate. Electric fields also can be employed in connection with capillary or nozzle feeds to produce electro sprays (Gomez, 1992; Bailey 1988). These types of atomizers are not normally used for

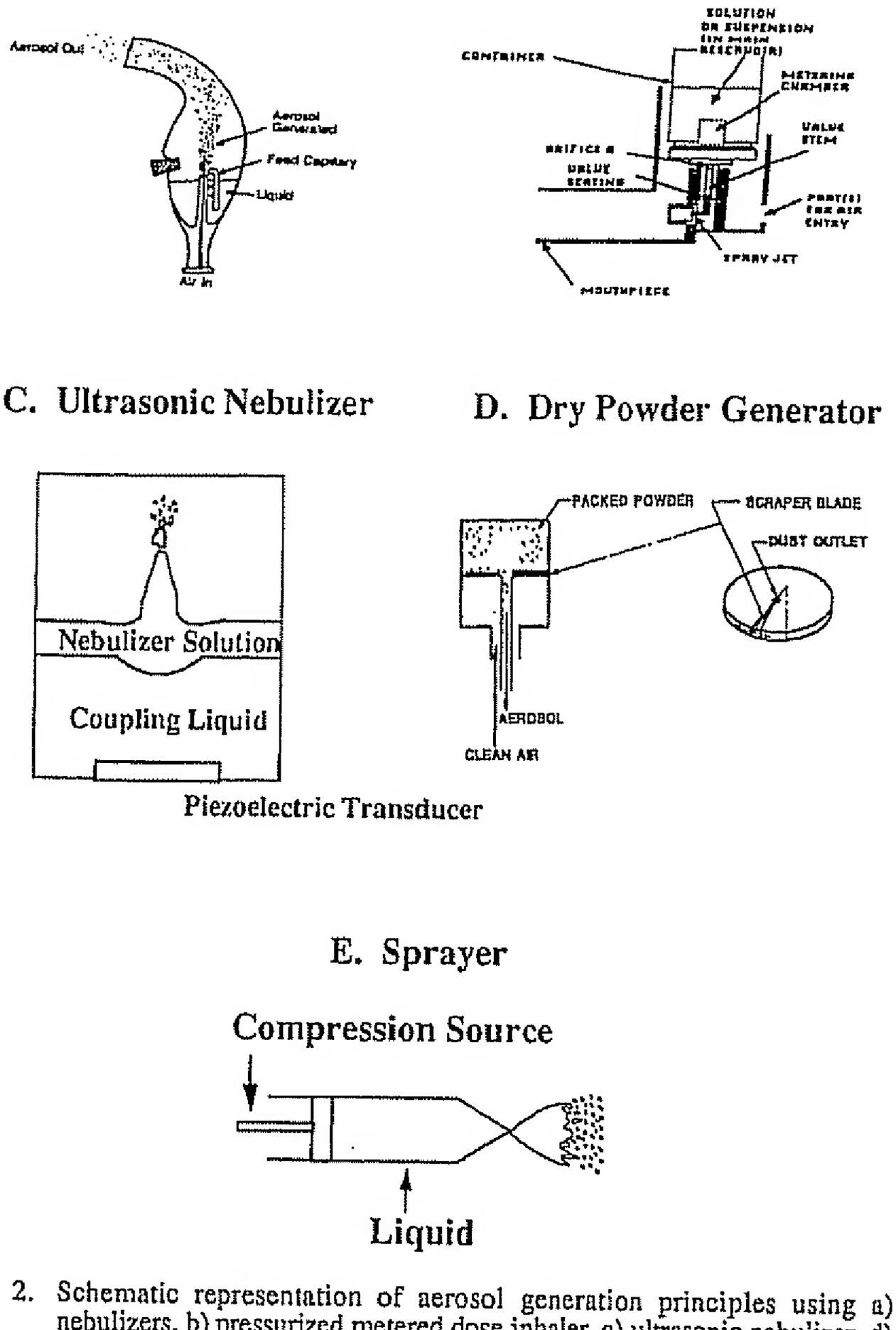

Figure 2. Schematic representation of aerosol generation principles using a) jet nebulizers, b) pressurized metered dose inhaler, c) ultrasonic nebulizer, d) dry powder generator, and e) sprayer.

inhalation purposes since they are often unable to generate sufficiently small droplet sizes. However, they are used in a number of nasal delivery systems.

A key feature of all methods of aerosol generation is that energy must be supplied to a liquid or powder in order to disperse it. This requirement is not a limiting problem for a device that can be used in a hospital or home setting where it does not have to be carried or be aesthetically pleasing to the patient. However, this need for an energy source does limit the options that are available for a practical device that can easily be used by out-patients. Ingenuity is needed to overcome this constraint in order to devise hand-held aerosol devices that are small enough to be convenient for the user.

c) Criteria for the Ideal Medical Inhaler

Ideal features of a medical aerosol inhaler would include the following:

-Reliability, reproducibility, accuracy
-Small particle size, 1-5 μm, for good respirability
-Simple to use and handle
-Small size - easy to carry
-Multiple dose capability
-Resistance to bacterial contamination
-Durability
-Cost effectiveness

All of these are desirable features, but the first three are essential. A medical aerosol inhaler must provide a consistent and reproducible release of pharmaceutical such that the amount of material inhaled is reproducible. The size distribution also must be small enough that an appreciable amount of aerosol can deposit in the lung with high efficiency and ease of use is a key factor that dictates compliance and correct useage. Available data on pulmonary deposition as function of particle size for mouth breathing humans indicate that the maximum efficiency is in the 2-3 μm mass median aerodynamic diameter range. Above 5 μm MMAD, pulmonary deposition decreases substantially (Schlesinger, 1985, 1988). Below 1 μm MMAD pulmonary deposition also decreases and it becomes more difficult to deliver particles with sufficient mass to be therapeutically effective. Therefore, it is desirable for medical aerosols to fall into the 1-5 μm MMAD size range.

It should be noted that these generalizations apply to data obtained using non-hygroscopic particles and controlled tidal breathing. Departure from these conditions will tend to invalidate the assumptions. For instance, inhalation of highly hygroscopic particles that grow rapidly in the high humidity of the airways, or rapid inspirations will results in more upper airway and less pulmonary deposition than predicted. It has been stated that aerosols less than 5 μm MMAD are "respirable". The respirable fraction of aerosols is a nebulous term and should be defined when used. One of the better definitions of respirable fraction has been recommended by The American Council of Governmental Industrial Hygienists (ACGIH) and this reads, "the fraction of an aerosol sample collected by a sampler whose size collection efficiency is described by a cumulative log normal function with a MMAD of 3.5 μm and a geometric standard deviation of 1.5" (Phalen et al., 1988).

No matter what generation technique is employed, the key factor is the size distribution. This dramatically influences deposition of particles in the respiratory tract and therefore determines inhaled dose and the subsequent pharmacological effect of the pharmaceutical. Thus, determination of the size distribution produced by a medical aerosol inhaler is an important part of the assessment of devices. Further, the specific sizing instruments, methodology, and sampling configuration are critically important in assessing performance and comparing different devices (Dolovich, 1991). Aerosols from medical inhalers are usually constantly changing as they proceed from the inhaler and invariably have not achieved an equilibrium size distribution by the time that they are deposited within the respiratory tract. Therefore, the specifics of how a size distribution is determined are critical to interpretation of data. In order to compare inhalers, it is best to use the same methodology with each inhaler. If this is not possible, the sampling methods and instrumentation should be clearly stated so that the measurements can be put into perspective and replicated, if possible.

CURRENT DEVELOPMENTS

With the basic principles developed above in mind, current developments are explored, as presented at the recent International Congress of Aerosols in Medicine. The information is grouped into the categories of propellant metered dose inhalers, dry powder inhalers, jet nebulizers, and alternative devices.

a) Propellant Metered Dose Inhalers

Although propellant inhalers have inherent disadvantages, such as a high spray velocity which leads to high oro-pharyngeal deposition, their advantages of ease of use, compactness, multi-dose capability, and user acceptance will mean that they are unlikely to be removed from the market place. Data provided by Shindoh et al., (1993) showed that the use of spacers can reduce particle size and alternate the effect of the high jet velocity in current MDIs. These data are in agreement with previous work by others (Newhouse and Dolovich, 1986). Sato et al., (1993) demonstrated that there was a positive correlation between the liquid aerosol droplet size and the chemical content of steroid in the aerosol from a suspension MDI. Results such as these lend confidence in using optical methods to size MDI aerosols when the sampling conditions are well defined.

New propellants are currently being evaluated. Two alternative propellants that appear promising are the hydrofluorocarbons HFC 134a (tetrafluoroethane) and HFC 227 (heptafluoropropane). Assuming that these propellants fulfil long term toxicity testing, then the remaining problem to overcome will be formulation development. HFC 134a has a high vapor pressure at room temperature of ≈75 psig and so standard canisters may have to be redesigned to fulfill safety requirements. More critically, all the presently approved dispersing agents, oleic acid, span 85, and lecithin are poorly soluble in the propellants and substitutes will be needed. Clearly, a great deal of research remains to be done.

As an example of some recent work, Keller and Ioset (1993) compared the in vitro performance of 134a and 227 with a CFC blend using the twin impinger. They demonstrated that, if formulated correctly with a cosolvent, the new propellants can produce comparable results to propellant mixtures of CFCs. (Table 1). There was a

TABLE 1.

Comparison of the average in-vitro deposition characteristics of various MDI-formulations driven by a CFC-blend, HFC 227 and HFC 134a*.

Batch No.		**B19-01**	**B18-01**	**B20-06**	**E06-01**	**E07-01**
Propellant	CFC-blend	227	227	227	134a	134a
Suspending agent	A	B	A	--	--	A
Co-solvent	--	++	++	++	++	++
% in-vitro deposition:†						
Rubber adapter (1)	2.4	3.9	3.7	2.7	5.7	5.3
Mouthpiece (2)	19.2	8.5	7.6	6.9	6.3	4.3
Oropharynx (3)	25.1	27.5	27.8	28.0	32.8	33.7
Upper resp. tract (4)	8.4	8.0	7.7	6.3	6.1	5.8
Lower resp. tract (5)	44.7	46.6	44.9	35.7	35.7	40.5
Sum of 1-5	100.1	94.5	91.7	74.4	86.6	89.6
Respirable fraction calc. as 100% of declared dose	44.7	49.6	48.8	48.5	41.2	46.3
Coefficient of variation (%)	(15.3)	(12.2)	(12.0)	(14)	(14.4)	(28.7)

*Results are the means of 3 x 10 actuations of MDI-batches stored at different conditions up to 12 months, each fired into the Twin Impinger, (Keller and Ioset, 1993)

† Expressed as a percentage of the declared dose for each canister.

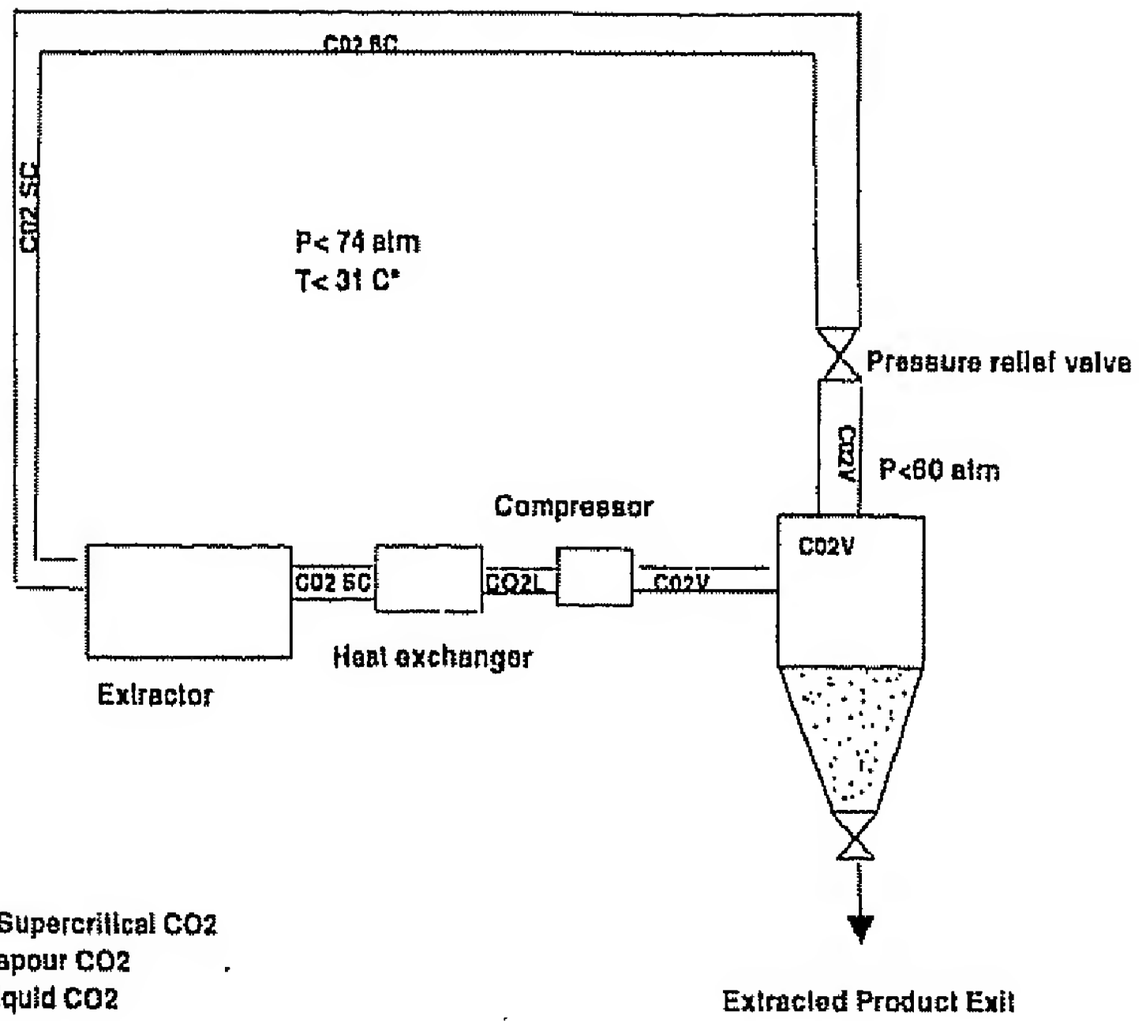

Figure 3. Extraction from MDI gaskets using supercritical fluids (Tcherevatchenkoff and Fourment, 1993).

tendency of the 134a formulations to deposit excess material in the glass bulb (oropharynx) of the twin impinger probably a consequence of the high vapor pressure of the 134a formulations relative to the 227 and CFC formulations. Output from the 134a formulations was also lower than expected, presumably due to adherence of active ingredient along the container walls.

Another related approach that circumvents the need for CFCs exploits the physical characteristics of supercritical fluids. The rubber gaskets that are an integral part of existing pressurized MDIs contain extractable components such as BHT. Presently, these gaskets are pre-extracted using CFC-11. Tcherevatchenkoff and Fourment (1993) describe an extraction method that utilizes supercritical CO_2 (Figure 3). At elevated temperatures and high pressure liquid CO_2 exhibits properties of low viscosity and high diffusivity. This allows materials such as BHT to be extracted from the rubber gaskets. The method, although more elaborate than the original technique, performs similarly to CFC-11 and does not appear to unduly affect the gaskets.

Finally, the use of current pressurized MDIs will continue for the near future at least. There is also a possibility that there may be exemptions in amendments to the Montreal Protocol that will allow the use of CFCs in medical inhalers based on relevant need. A useful advance for pressurized MDIs is the introduction of a breath actuated feature in the 3M Autohaler. This change circumvents the problem of coordinating inhalation with the actuation of pressurized MDIs and considerably simplifies and improves their convenience. If this device is robust and reliable over long use it should be useful.

b) Dry Powder Inhalers

Dry powder inhalers avoid the use of CFCs. However, the history of dry powder inhalers (DPIs) predates the recognition that many CFCs are harmful to the atmosphere. The first of these inhalers was the Spinhaler introduced by Fisons in the early 1960's. This was followed by the Rotahaler (Glaxo) and more recently the Turbuhaler (Astra) and the Diskhaler (Glaxo) have been introduced. The latter two devices are more advanced in terms of their multi-dose capability. The Spinhaler and Rotahaler require patients to place individual capsules in the device before activating. Unfortunately, all these devices are highly dependent upon the patients inhalation pattern. To optimize deposition in the

deep lung, a slow deep breath is recommended followed by a period of breath holding. However, to efficiently remove powder from these devices and to deaggregate powder agglomerates requires a rapid inhalation. Consequently, high oropharyngeal deposition is likely. To improve the flow properties, a carrier molecule and bulking agent, usually lactose, is required of a median particle size around 50-100 μm (Bell et al., 1971). Although this allows more dose to be dispensed, it still requires that the powder reaching the oral cavity should efficiently separate the small particles of active drug from the large particles of carrier; this may not occur. The Turbuhaler (Wetterlin, 1988) avoids this problem and uses no carrier. However, the baffle system that the device uses to introduce turbulence to the air stream causes much of the dose to remain within the device. Overall, the dose variability and poor efficiency of these devices restricts the number of potential compounds that could be used with them. This is particularly relevant to the delivery of proteins and peptides where a narrow therapeutic window may exist that requires reproducible dosing. In addition, the cost of proteins may necessitate improved dose efficiency to be able to compete with other routes of administration.

The available information indicates that particle size distributions from current dry powder inhalers are in a similar range to those of pressurized MDIs. Clinical effects from dry powder and MDI aerosols seem roughly comparable with available formulations (Hetzel and Clark, 1977; Persson et al., 1981). There is a suggestion from the available data that overall efficiency of delivery may be somewhat lower with dry powder inhalers compared to MDIs in that up to twice as much nominal dose delivered from the inhaler may be needed for an equivalent clinical result. Limited data are available on dose distribution from the use of dry powder inhalers (Newman et al., 1988; Vidgren et al., 1988, 1990). One paper (Vidgren et al., 1988), employing a radiolabel on an altered form of dry powder (spray dry technique), indicated a slightly improved dose distribution with a dry powder inhaler. One might expect a possible improvement in dose distribution from dry powder inhalers with similar particular size distributions to pressurized MDIs because the high velocity jet delivery of pressurized MDIs is absent in dry powder inhalers. However, the fact that higher inhalation flow rates may be required by the patient or that aggregated particles may be adequately dispersed may counter this advantage.

A search of the patent literature will show that the next generation of powder devices are not very far from being introduced. One of the key advantages of these devices will be a much improved dosing efficiency. One, described by Corbett et al. (1993), uses the principle upon which a number of existing dust feeder instruments are based (including the Turbuhaler). Namely, it uses a powder compact. A single surface is exposed from which metered powder doses are removed and aerosolized, as opposed to the continuous abrasion of the surface that some dust feeders apply. With this device, slices from the compact surface are removed by a helical blade (Figure 4). The level of compaction and uniformity of dose within the compacted powder were predetermined through experimentation and maintained by pressure exerted from a coiled spring. One nice feature of the inhaler is that it contains a vane that prevents water vapor in exhaled breath from reaching the powder. However, the very nature of the inhaler makes it difficult to seal from moisture altogether. The unit is compact and is likely to be relatively inexpensive. The performance of the device was evaluated in vitro as well as in vivo where plasma concentration vs. time profiles generated with the DPI and a pressurized MDI were illustrated. The in vivo results show that the performance is comparable to that achieved with a current pressurized MDI. The limitation of the device is the same for existing powder inhalers. That is, dependence upon the inhalation flow rate generated by the patient. However, the device does appear to overcome the major problem of dose dispensed to the patient. This was always maintained within 25% of the label claim (Figure 5).

The Easyhaler, a new multiple dose powder inhaler, was evaluated in asthmatic patients and healthy volunteers (Vidgren et al., 1993). Pulmonary deposition of Tc^{99m}-DTPA labeled powder was monitored by gamma camera. This was found to be 28.9±11.6% for the normal volunteers and 23.7±6.2% in the asthmatic patients. Only 6 to 7% of the initial dose remained in the device after actuation. This type of determination of delivered dose to the lung in patients is highly desirable to characterize the actual performance of new devices in clinical use. The Easyhaler was also constructed in a fashion that provides some flow restriction so that the peak inspiratory flow is relatively independent of inspiratory effort. The Easyhaler also shares the

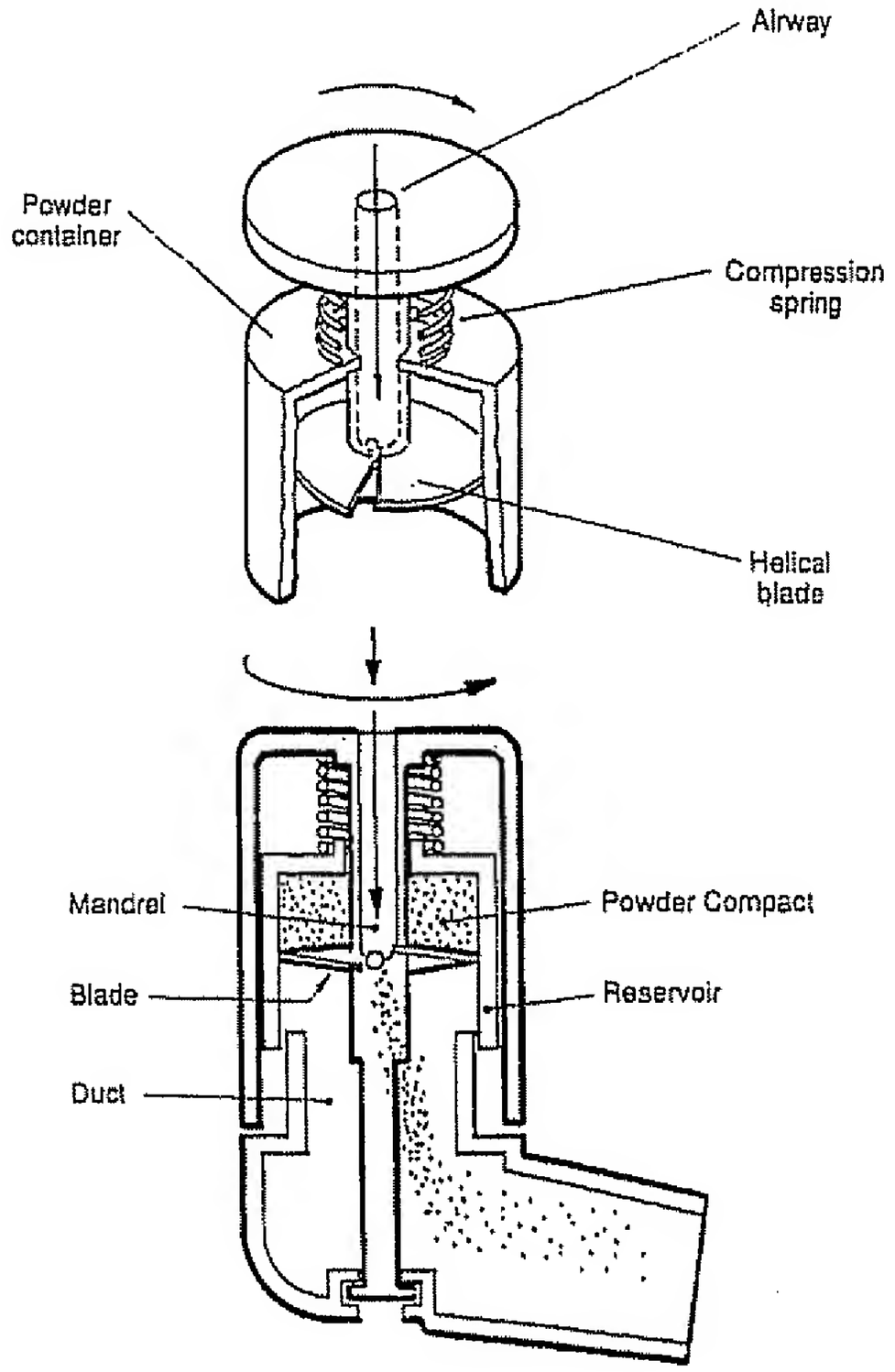

Figure 4. Rotary planer basic concepts (Corbett et al., 1993).

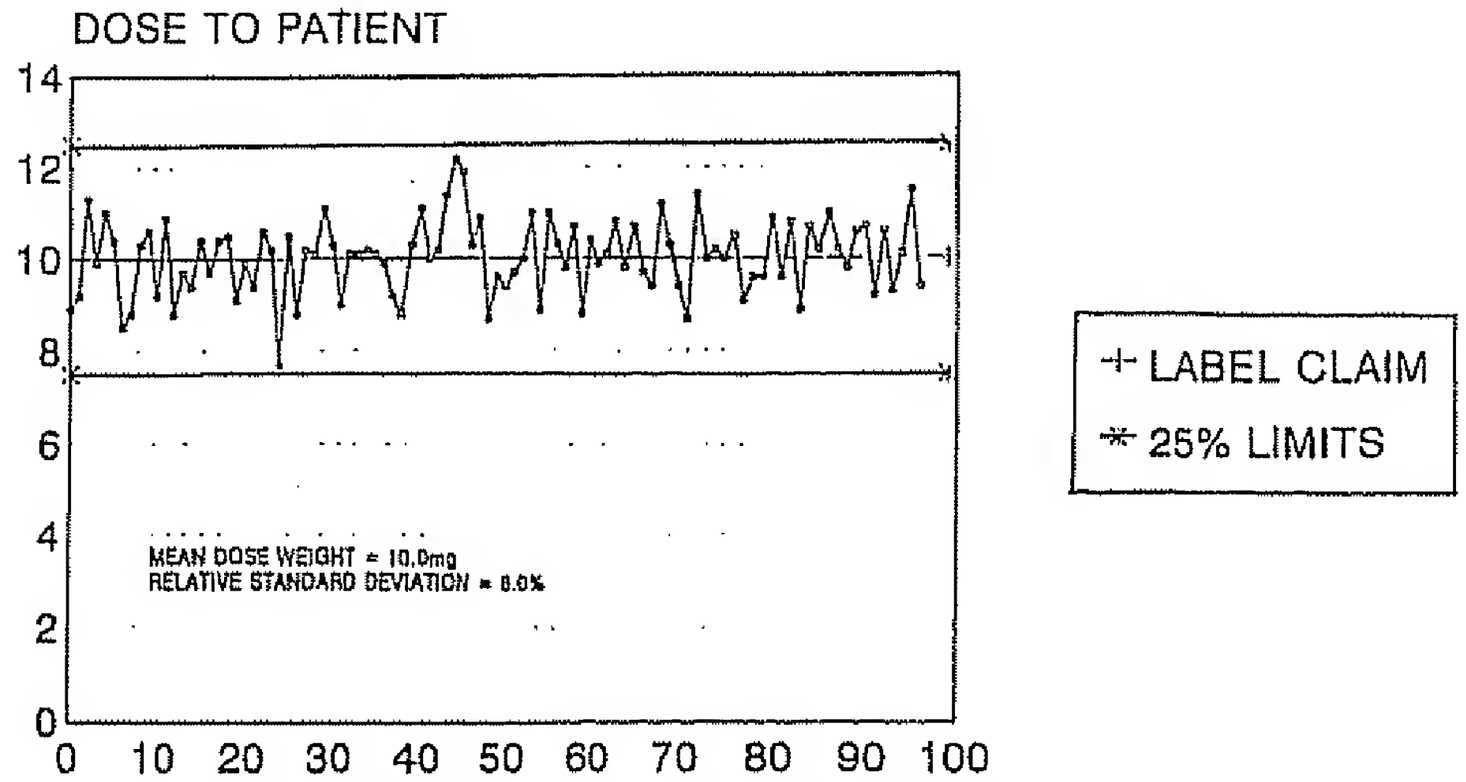

Figure 5. Dose uniformity from a rotary planer prototype (Corbett et al., 1993).

limitation that a powder reservoir may be susceptible to moisture contanimation. All dry powder devices which use dispensing reservoirs have to deal with this issue.

c) Jet Nebulizers

The advantage of nebulizing solutions is that the process is simple to perform and a wide range of compounds can be inhaled in this manner. Unlike the propellant and powder inhalers they are continuous use devices and require patients to inhale for periods of 10-20 minutes. Since exhalation totals ≈60% of the respiratory cycle this means that the devices are inherently wasteful. One method of avoiding this problem is to utilize the nebulizers in a dosimetric fashion. Nikander et al. (1993) evaluated the performance of a jet nebulizer vs. ultrasonic nebulizer (Spira) vs. MDI (Astra) in asthmatic children. They compared dosimetric vs. continuous nebulization and nebulization with and without a spacer device. Dosimetric operation was controlled electronically. The nebulizer was triggered only at the initiation of inhalation. The inhaled mass of drug (budesonide) was determined by interposing a filter between the nebulizer and the patients face mask. The exhaled mass (that which doesn't deposit on the inhalation filter) was assessed by the deposition on 1 or 2 exhalation filters. The authors concluded that dosimetric nebulization was the most efficient system for use with budesonide suspensions in children. (Figure 6).

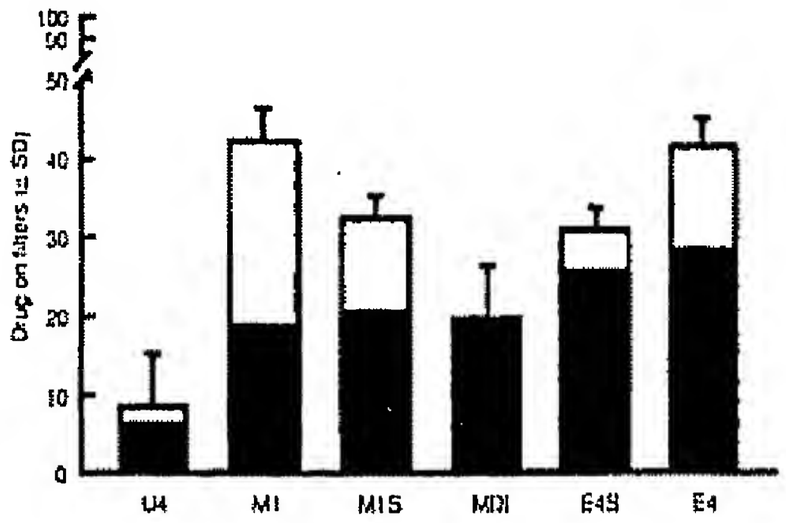

Figure 6. The total output, inhalation (■) and exhalation (□) filters, in percent of nominal dose by inhalation system (Nikander et al., 1993). [U4 - dosimetric ultrasonic nebulization; M1 - continuous jet nebulization, MIS - continuous jet nebulization with spacer; MDI - MDI with Nebulaher; E4S - dosimetric jet nebulization with inspiratory spacer; E4 - dosimetric jet nebulization]

Other disadvantages of most current nebulizers include output variability between units; large dead volumes and variation in solution vs. solvent output. The particle size and size distribution should also fall within certain limits, otherwise lung deposition will be compromised. A variety of nebulizers available in the USA were classified according to most of the listed criteria (Lux et al., 1993). No nebulizer was found to dominate in all criteria, although the Sidestream nebulizer appeared to perform better than average, particularly in terms of output rate and particle size distribution (Table 2). Another nebulizer, the Parl IS-2, which is available in Europe, was evaluated by Knoch et al. (1993). It has the notable advantage of minimizing the dead volume at the end of nebulization. The reservoir forms a cone with the point downwards adjacent to the liquid feed intake. Despite these improvements in design the nebulizer has not undergone significant change since the time of its inception over 100 years ago. It can be expected that more complex solution and suspension formulations will be nebulized in the future. These types of formulations and also many proteins may be affected by the process of aerosol generation. Nebulizers reflux 99+% of the nebulizer fluid, this also means that the solution will be repeatedly aerosolized over time and only a small fraction of the gross aerosol produced within the nebulizer will escape as inhalable aerosol; therefore, any damage will amass over time. In addition, the shear forces required to produce the droplets may add to any observed degradation. Finally, there is a risk of chemical reactions being enhanced by aerosolization simply through the huge air:water interface that is repeatedly generated.

TABLE 2.

Comparison of Jet Nebulizers (Lux et al., 1993).

Nebulizer Model	Rank by Unit to Unit Variability	Rank by Output	Rank by Dead Volume	% Mass < 5 m	% Drug Aerosolized	% Solution Lost as Vapor
Sidestream	7	1	1	95	44	17
Salter	1	2	11	66	36	5
Raindrop	4	7	9	86	26	7
RCI	3	3	5	72		
Acorn	5	8	2	72		
Whisper	6	4	7	65		
Misty	8	5	6	73		
Ava	10	6	4			
Inspiron	2	9	10			
Fanjet	9	11	3			
WeeNeb	11	10	8			

Some other theoretical aspects of nebulization were described by Phipps and Gonda (1993). They examined the effects of solution temperature and humidity of air on the droplet size and solute concentration emerging from a nebulizer. The results were compared to those expected from theoretical models assuming ideal solution behavior. This resulted in large deviations from the observed results. Empirical formulae gave a better correlation with observations especially when the connection tubing between nebulizer and mouthpiece was lengthened to allow equilibrium to be reached between vapor and droplet.

An alternative method of calculating droplet size using cascade impaction was presented by Gebhart et al. (1993). These authors utilized the "residual" technique to estimate droplet size. This method requires that the droplets be dried prior to entering a cascade impactor (Figure 7). Estimations of the initial droplet size are then calculated using the particle size determined from impaction and knowledge of the initial solution concentration. They subsequently use this technique to estimate the droplet size produced by several nebulizers and the fraction that they expect to reach the intrathoracic regions of the lung. The fractions were estimated from a cutoff value of 6 μm. In turn, this size was based on the results of theoretical and experimental observations of lung deposition. They found that the Pari IS-2 produced the highest mass output/min that would deposit in the intrathoracic regions of the lung.

The previous two studies illustrate the dynamics of droplet behavior and demonstrate the difficulty of estimating meaningful droplet sizes. What is a meaningful droplet size? First, the goal must be defined. Deposition in the upper, lower or throughout the respiratory tract? Generally, the target is the lower respiratory tract. With a fixed objective in mind, one can then argue that the droplet/particle size that dictates deposition in the lower respiratory tract is the one that exists the instant before deposition. It is usually not possible to make this measurement directly. Therefore, extrapolations must be made to determine what an appropriate droplet size is at a given point in time prior to entering the mouth, that will ensure deposition in the deep lung. The determination of this size will also be dependent upon the measuring technique. It is quite possible for two techniques to give two different sizes for the same droplets. For example, a laser measuring a median droplet size of 2 μm and the residual technique giving 5 μm may both be correct and both sizes may be appropriate. The residual technique provides an absolute method of estimating droplet size for a nebulizer since it measures the size of droplets which escape the nebulizer at the instant of their formation.

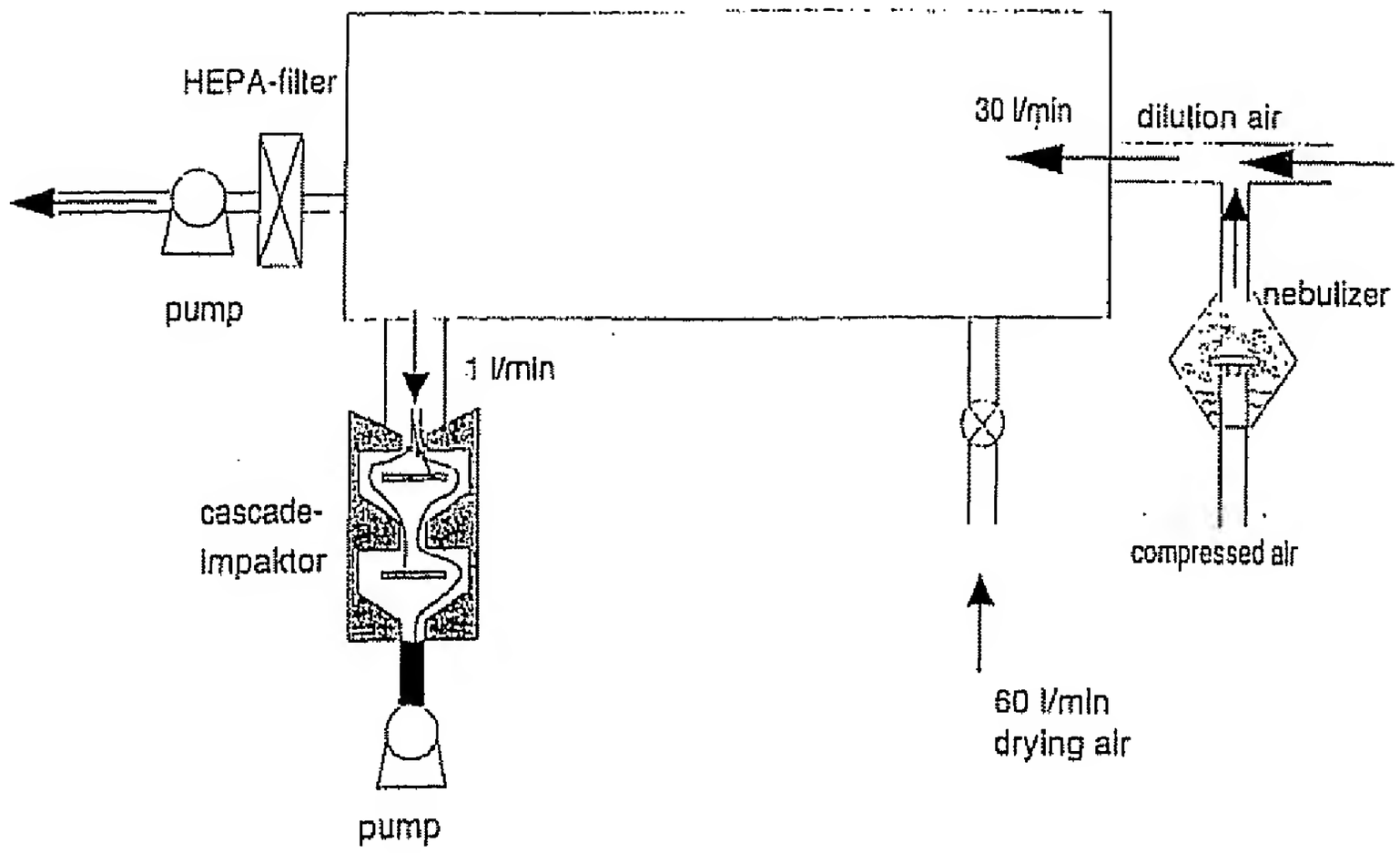

Figure 7. Schematic of aerosol sizing configuration using residual technique (Gebhart et al., 1993).

The point of formation may be within the nebulizer reservoir (primary formation) or after a collision of droplets prior to deposition within the impactor (secondary formation). Laser techniques provide a dynamic method of estimating a droplet size at a given point in time and space, usually well after the droplet has left the nebulizer. Therefore, it is quite reasonable to expect two different but correct results. Estimating whether a new generation technique is adequate for efficient lung deposition, by in vitro methods is therefore also dependent upon the measurement technique.

d) Alternative Devices

Recently, some efforts have been directed towards developing aqueous systems that dispense bolus doses of solution. The Respimat (Boehringer Ingelheim) is one elegant example that uses this principle. A micro droplet of solution is dispensed onto an ultrasonic plate. This vibrates at high frequency causing the fluid to be aerosolized. This device is also an excellent example of the use of new technology to miniaturize devices which have previously been too big for ambulatory outpatient use. Unfortunately, large power requirements have restricted its use to date. Ilgen and Hollander (1993) showed that the particle size distribution from the Respimal was qualitatively similar to that obtained from a jet nebulizer.

Jager-Waldau (1993) described the performance of a prototype multi-dose aqueous spray inhaler. The inhaler utilizes manually compressed air to atomize a metered dose of solution (Figure 8). The droplets are produced by the device within a mixing chamber containing a polyurethane sponge. 10-15 µl of solution dose is dispersed within the sponge by a metering pump. The solution is then atomized by the air passing through the sponge pores. Droplets sizes estimated by the Malvern Mastersizer were 10 to 20 µm. Droplet sizes were a function of the liquid to air volume ratios. The present prototype has a number of limitations including the use of a sponge as a surface from which to generate aerosol. Nonuniformity in the sponge matrix also will lead to differences in the size output and the dispensed volume. Droplet sizes, although large, may be reduced through time or the use of some form of spacer device. Residual fluid left in the mixing chamber between dosing times also will encourage bacterial growth.

Another ingenious device described by Baum et al. (1993) utilizes ultrasonic energy in a novel fashion. Rather than use the high frequency energy to aerosolize fluid, the ultrasonic pressure cycles are used to force a metered solution dose of drug through a grid of microscopic nozzles ≈4 µm in diameter. The dispensed droplets are introduced

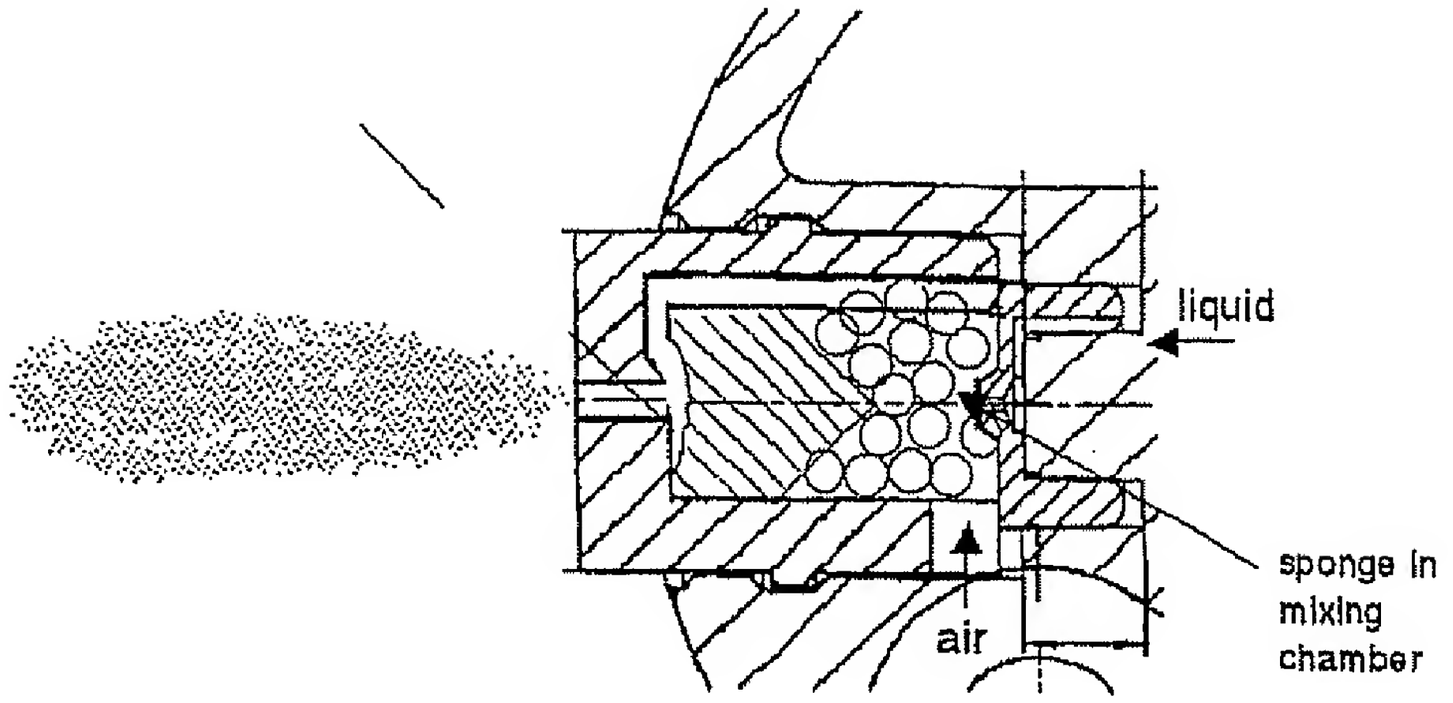

Figure 8. Nozzle design for internal mixing of liquid and gas (Jager-Waldau, 1993).

into an air cross flow generated by inhalation (Figure 9). Cartridges containing sachets of liquid with 100+ doses can be added to the main body of the device. The unit is battery operated. Potential problems associated with such a device may be with production of the preformed nozzles and clogging of nozzles after repeated use. However, this will also be drug and formulation dependent. The cost of the device is also likely to be substantially greater than existing devices.

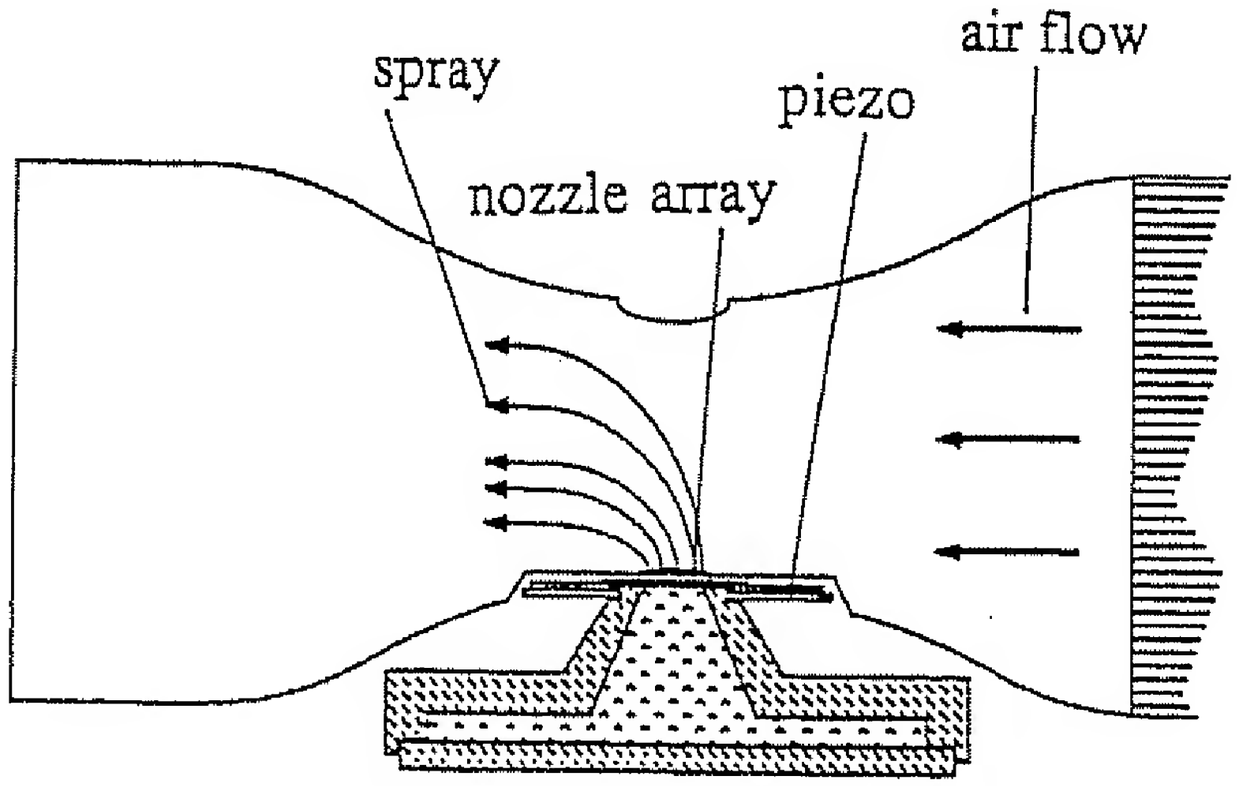

Figure 9. Schematic of breath actuated piezoelectric inhaler (Baum et al., 1993).

One of the limiting factors with these aqueous systems may be the need for preservatives to inhibit bacterial contamination of the liquid contents. Since these components are not approved excipients for inhalation use, a series of toxicology studies will be necessary before such devices can ultimately be brought to the market place.

Nevertheless, these and other technological advances will continue to be made. Key factors in success will be improved performance characteristics that are value-added to the user, while providing reliable, simple operation in an affordable device.

III. SUMMARY

It is clear that medical devices used to generate aerosols are in a period of transition. The propellant metered dose inhalers have by far been the most widely used

device over the last 25 years. The use of nebulizers has remained associated with hospital use and some home therapy and this is not likely to change. On the other hand, significant advances in dry powder technology can be expected in the next few years and the dominance of the propellant inhaler will be challenged while a transition is made from pressurized MDI formulations using old propellants to formulations using alternative propellants. Aqueous bolus dose systems are also expected to emerge. The sum of these effects suggests that there will be a variety of novel inhaler types available in the near future and pressurized MDIs will not be as dominant as they have been in the past. The overall outlook for inhaler therapy is positive and this is exemplified by some of the examples that have been described herein. Future devices will afford patients with highly efficient and reproducible dosing mechanisms that will be cost effective and in some circumstances will provide new systemic therapies that avoid the need for parenteral administration. Ingenuity, good engineering, cost, and attention to patient needs for optimal inhalation delivery, will be the determinants in improving medical aerosol devices.

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Reviewed by:
Myrna Dolovich, P Eng

Address reprint requests to:
Ronald K. Wolff, PhD
Lilly Research Laboratories
P.O. Box 708
Greenfield, IN 46140